REMARKS

Status of the Claims

Upon entry of this amendment, claims 1-22 will be pending in the application. By this amendment, claims 7 and 14 have been amended. Support for these amendments can be found throughout the specification, e.g., at page 7, l. 3 to l. 11. The amendments presented solely for the purpose of clarity or consistency of claim language unless otherwise noted. No new matter has been added by this amendment.

Applicants acknowledge that the Office has reconsidered and withdrawn the objection to claim 21 presented in the previous Office Action Paper No. 6.

Patentability Under 35 USC § 112

Applicants acknowledge that the rejection of claim 21 for alleged indefiniteness in the recitation of the term "scopolamine free base plasma concentration is achieved . . .." has been reconsidered by the Office and withdrawn.

Claims 7, 14, 17-18, and 21 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly using the indefinite expression "a chemically modified equivalent" or "chemically modified equivalents."

While Applicants maintain traverse of the foregoing rejections, it is respectfully submitted that these rejections are obviated by the amendments to the claims herein. These amendments are presented solely for clarity. Applicants do not acquiesce to the asserted merits of the rejection. Further, Applicants reserve the right to pursue claims in a related application to all subject matter that may be considered withdrawn from prosecution in the instant application.

Patentability Under 35 USC § 103

Claims 1-21 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Keith (WO 83/00286) in view of Osol et al. (Remington's Pharmaceutical Sciences, 15th ed., 1975). Applicants respectfully traverse the stated grounds of rejection and submit that the subject invention is neither disclosed nor practically suggested by the teachings of cited references considered in combination.

The Office relies on Keith for allegedly disclosing an aerosol nasal spray vehicle (which the Office asserts to generically encompass "pharmaceutical acceptable carriers") and a scopolamine salt such as scopolamine hydrochloride. The Office further states that:

> Keith's reference is seen to clearly provide the motivation to modify the spray composition by employing similar aerosol spray vehicle or pharmaceutically acceptable carriers such as polyvinyl alcohol, gelling agents, bioadhesives, thickening agents, and surfactants herein.

No basis for this assertion is provided by the Examiner. Nowhere in the record is there presented a practical suggestion or motivation in Keith to evaluate other useful "pharmaceutical acceptable carriers", and the Keith reference actually teaches away from this endeavor by disclosing a particularly preferred carrier for a scopolamine spray formulation.

In particular, Keith discloses an aerosol spray nasal composition comprising a major amount of an aerosol spray vehicle and scopolamine hydrochloride. The specific formulation disclosed by Keith is limited to an aqueous solution of scopolamine hydrochloride in a stock solution of 20% alcohol in water (see, for example, WO 83/00286, at page 3, Example I). Keith clearly fails to discuss generic pharmaceutical carriers in a manner that would suggest specific modifications or improvements to the disclosed compositions. In particular, Keith makes no reference to the usefulness or identification of emulsifying or suspending agents, and most certainly fails to suggest polyvinyl alcohol as a substitute for a "pharmaceutically acceptable carrier" in the generic/specific context asserted by the Examiner.

The deficiencies of Keith are not remedied by the secondary disclosure of Osol et al. This reference sets forth an extensive laundry list of emulsifying and suspending agents--of which polyvinyl alcohol is but one agent among many. There is clearly no suggestion in either reference to utilize such an agent in an intranasal scopolamine formulation.

Contrary to the Examiner's position, Osol et al. specifically define polyvinyl alcohol as an "emulsifying and suspending agent"—as distinguished from a generic "carrier" that the Office argues is disclosed by Keith. The "carrier" of Keith, however, is limited to an alcohol plus water formulation, whereas Osol et al. specifically teach the use of emulsifying and suspending agents:

> [T]o overcome agglomeration of the dispersed particles, and to increase the viscosity of the medium . . .

Thus, even if Keith et al. suggested a generic utility for alternative "carriers", such would not fit the definition provided by Osol et al. (introductory paragraph) for an "emulsifying and suspending agent".

Regardless of whether Keith et al. teach a generic "carrier", the reference clearly teaches away from selecting an emulsifying or suspending agent as disclosed by Osol et al. In particular, the latter agents are specifically disclosed for "prevention of agglomeration of particles, or increased viscosity". Keith's formulation employs a "spray vehicle" for scopolamine that comprises water and ethanol. Accordingly, Keith et al. teaches addition of a viscosity-lowering excipient to water to enhance scopolamine delivery in an intranasal formulation. The artisan would therefore be led directly away from the path suggested by the Office—i.e., allegedly to improve the Keith et al. formulation by adding an "emulsifying and suspending agent" as described by Osol et al.

Also notable is the teaching of Osol et al. that emulsifying or suspending agents are useful to "overcome agglomeration of . . . dispersed particles." No such desired utility is disclosed in Keith, and it is not believed that scopolamine has a tendency of "agglomeration" of particles that would suggest employment of any of these agents in an intranasal scopolamine formulation.

In view of the foregoing, the record is clear that Keith taken in combination fails to teach or suggest the desirability of using an emulsifying or suspending agent, and particularly polyvinyl alcohol, in an intranasal scopolamine formulation.

With regard to more specific aspects of the invention presented in the claims, these aspects are respectfully submitted to be patentable in view of the foregoing arguments (e.g., based on patentability of independent claim 1). Moreover, the record further evinces that Keith in view of Osol et al. fail to teach more specific aspects of the invention embodied in the dependent claims.

In particular, the primary and secondary references fail to teach or suggest scopolamine in a pharmaceutically acceptable carrier comprising polyvinyl alcohol at a particular pH value or buffer salt concentration as presently claimed. Specifically, Keith in view of Osol et al. do not teach or suggest an intranasal scopolamine formulation at a pH below about 4.0, much less at a pH below about 3.5, nor at a salt concentration below about 200 mM.

With regard to Applicants' selection of polyvinyl alcohol as a carrier for scopolamine, in a formulation having a pH below about 4.0 or 3.5, this combination of features clearly provides unexpected results over the art of record. In particular, it was widely known in the art that polyvinyl alcohol should be used in a pH range of about 5-8. Enclosed herewith is an excerpt from the *Handbook of Pharmaceutical Excipients*, 2nd Edition, page 383. As noted at paragraph 9 under "Pharmacopeial Specifications", the indicated pH for polyvinyl alcohol is between 5.0 and 8.0. Below this section, under the heading "Incompatibilities", the reference cautions that "[p]olyvinyl alcohol decomposes in strong acids and softens or dissolves in weak acids or alkalis."

This express disclosure of the *Handbook of Pharmaceutical Excipients*, 2nd Edition, teaching a pH range for polyvinyl alcohol far outside of Applicants' claimed pH range, renders the claimed combination nonobvious.

The Office further argues that Applicants make an "admission" in their specification that a pH range of below 4.0 is described in the prior art for the claimed intranasal scopolamine formulations. U.S. patent application 07/765,615 is discussed in

the Background section of Applicants' specification at page 3, lines 17-22) . The scopolamine formulations of this reference are spray formulations at a pH of "4+/-0.2". Applicants' Background section notes that this formulation is inherently inefficient and requires high dosages (0.4 mg/ml of scopolamine per dose) that are wasteful of drug and add costs as well as undesirable side effects (See specification, p. 3, l. 19-22).

Applicants' novel pH value is "below about 4.0", or "below about 3.5." It is submitted that all of Applicants' pH values are distinguished over U.S. patent application 07/765,615 ('615 application). Moreover, it is abundantly clear that Applicants' formulation, including polyvinyl alcohol which is taught to have an "indicated pH . . . between 5.0 and 8.0" is further distinguished from the art of record at the claimed pH values.

In the context of pH, the disclosure of the '615 application underscores the failure of the art of record to teach or suggest a combination of polyvinyl alcohol in a formulation as disclosed by Keith. If one follows the teachings of the '615 application concerning pH (i.e., by selecting a mildly acidic pH of 4.0 for an aqueous/ethanol scopolamine formulation as disclosed by Keith), one would have been directly led away from selecting polyvinyl alcohol as a "carrier" based on the indicated range of pH of this emulsifier in the range of "between 5.0 and 8.0."

Lastly, the art of record is deficient of any teachings regarding a buffer salt concentration range of an intranasal scopolamine below about 200 mM. The Office Action presents no evidence or arguments to the contrary, and it is noted above that the '615 application teaches a clearly distinct range of 0.4 mg/ml of scopolamine per dose. Thus, in this aspect also Applicants' invention can be seen to provide unexpected results.

Based on the evidence and arguments presented herein above, Applicants respectfully request that the rejection of claims 1-21 under 35 U.S.C. § 103(a) over Keith in view of Osol et al. be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Date: January 16, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please amend claims 7 and 14 as follows. Please add new claim 22 as follows.

7. (Amended) An intranasal formulation as in claim 1, wherein said scopolamine is provided as a chemically modified equivalent selected from scopolamine bromide, scopolammonium bromide, scopolamine hydrochloride, methscopolamine bromide, or methscopolamine nitrate, or a pharmaceutically acceptable salt thereof.

14. (Twice Amended) A method of preventing and/or treating nausea and/or vomiting comprising administering intranasally to a mammal an effective amount of scopolamine [, or a chemically modified equivalent] or a pharmaceutical salt thereof in a pharmaceutically acceptable carrier at a pH below about 4.0 and a buffer salt concentration below about 200 mM, said carrier incorporating polyvinyl alcohol.

22. (New) The method of claim 14, wherein said scopolamine is provided as a chemically modified equivalent selected from scopolamine bromide, scopolammonium bromide, scopolamine hydrochloride, methscopolamine bromide, or methscopolamine nitrate, or said pharmaceutically acceptable salt thereof.

Polyvinyl Alcohol

1. Nonproprietary Names

USP: Polyvinyl alcohol

2. Synonyms

Airvol; *Elvanol*; *Polyviol*; *Poval*; PVA; vinyl alcohol polymer.

3. Chemical Name and CAS Registry Number

Ethenol, homopolymer [9002-89-5]

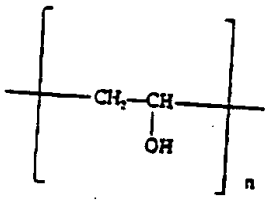
4. Empirical Formula Molecular Weight

$(C_2H_4O)_n$ 30 000-20 0000

Polyvinyl alcohol is a polymer in which the average value of n lies between 500-5000. Various grades with different viscosities and molecular weights are commercially available; typical values are shown below.

Grade	Molecular weight
High viscosity	≈ 200 000
Medium viscosity	≈ 130 000
Low viscosity	≈ 30 000

5. Structural Formula



6. Functional Category

Coating agent; nonionic surfactant; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Polyvinyl alcohol is used primarily in topical pharmaceutical formulations, particularly ophthalmic products.[1-3] It is a nonionic surfactant and is used as a stabilizing agent for emulsions. Polyvinyl alcohol is also used as a viscosity-increasing agent, especially in ophthalmic products, where it is generally preferable to have slightly viscous formulations. Polyvinyl alcohol also has desirable lubricant properties which are utilized in many ophthalmic products such as artificial tears and contact lens solutions.

Polyvinyl alcohol is additionally used in the preparation of various jellies which dry rapidly when applied to the skin. It is also used in the preparation of sustained release tablet formulations,[4] and in transdermal patches.[5]

Cross-linked polyvinyl alcohol microspheres, used for the controlled release of oral drugs, may be prepared by mixing 30% aqueous polyvinyl alcohol solution with an active drug and glutaraldehyde solution.[6] Cross-linked polyvinyl alcohol hydrogels[7] may also be formed by repeated freezing and thawing of polyvinyl alcohol solutions.[8]

Polyvinyl alcohol is also used in cosmetics.

Use	Concentration (%)
Emulsions	0.5
Ophthalmic formulations	0.25-3.0
Topical lotions	2.5

8. Description

Polyvinyl alcohol occurs as an odorless, white to cream-colored granular powder.

9. Pharmacopeial Specifications

Test	USP XXII (Suppl 6)
Viscosity	+
pH (4% aqueous solution)	5.0-8.0
Loss on drying	≤ 5.0%
Residue on ignition	≤ 2.0%
Water-insoluble substances	≤ 0.1%
Organic volatile impurities	+
Degree of hydrolysis	85-89%

10. Typical Properties

Melting point:
228°C for fully hydrolyzed grades;
180-190°C for partially hydrolyzed grades.
Refractive index: n_D^{25} = 1.49-1.53
Solubility: soluble in hot or cold water; solubility in water increases as the molecular weight decreases. Effective dissolution of partially hydrolyzed grades requires the dispersion and continued mixing of the solid in cold or tepid water followed by sustained heating at 85-95°C until dissolved. Very slightly soluble in some polyhydroxy compounds, certain amines and amides. Practically insoluble in aliphatic, aromatic and chlorinated hydrocarbons, esters, ketones, and oils.
Specific gravity:
1.19-1.31 for solid at 25°C;
1.02 for 10% w/v aqueous solution at 25°C.
Specific heat: 1.67 J/g (0.4 cal/g)
Viscosity (dynamic):

Grade	Dynamic viscosity of 4% w/w aqueous solution at 20°C (mPa s)
High viscosity	40-65
Medium viscosity	21-33
Low viscosity	4-7

11. Stability and Storage Conditions

Polyvinyl alcohol undergoes slow degradation at 100°C and rapid degradation at 200°C; it is stable on exposure to light. Aqueous solutions are stable and should be stored in corrosion-resistant containers. For extended storage periods, an antimicrobial preservative should be added to polyvinyl alcohol solutions.

The bulk material should be stored in a well-closed container, in a cool, dry, place.

12. Incompatibilities

Polyvinyl alcohol will undergo reactions typical of a compound with secondary hydroxy groups, such as esterification.

Polyvinyl alcohol decomposes in strong acids and softens or dissolves in weak acids and alkalis. Incompatible at high